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Introductory Chapter: Autonomic Nervous System - What We Know About It

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1. Introduction

The nervous system captures and processes stimuli acting on an organism and provides the means for an adequate response. It provides neural control that is faster than hormonal pathways and is, therefore, more suitable for transmitting information that requires a rapid, coordinated response. The sensory, somatic, and autonomic parts of the nervous system have been extensively studied. What is the physiology of the autonomic nervous system and what do we teach students about this system in medical faculties?

The autonomic (vegetative) nervous system is an involuntary system that primarily controls and modulates the functions of the visceral organs. Similarly, through the control of somatic functions, a relatively large part of autonomic regulation is controlled through the reflex arc. The autonomic nervous system innervates the smooth muscles of vessels, digestive system, bladder and urethra, lower airways, cardiac muscle, sweat and lacrimal glands, and adrenal medulla. The autonomic nervous system has three branches: sympathetic, parasympathetic, and enteric [1–4]. In many cases, the sympathetic and parasympathetic nervous systems have "opposite" actions, in which one system activates and the other inhibits a physiological response. The current view is that the sympathetic nervous system is a "quick response mobilizing system" and the parasympathetic nervous system is a "more slowly activated inhibitory system."

The enteric—or intrinsic—nervous system is one of the main divisions of the autonomic nervous system and consists of a network of neurons that manage the functions of the gastro-intestinal tract [5]. It is capable of acting independently of the sympathetic and parasympathetic nervous systems; however, it may be modulated by sympathetic and parasympathetic activity. The main components are the plexus myentericus (Auerbach), which mainly influences motility, and the plexus submucosus (Meissner), which is responsible for glandular secretions [6]. The enteric nervous system has also been referred to as the "second brain" [7].

2. Composition

The composition of the efferent pathway is the same for both the sympathetic and parasympathetic divisions. It consists of two types of neurons:

- The first type is located in the brain stem or spinal cord and is referred to as *preganglionic* neurons.

- The second type is located in the ganglia, or in the body itself, and is referred to as *postganglionic* neurons.

3. Parasympathetic division

From an anatomical perspective, the parasympathetic division is the craniosacral component of the autonomic nervous system. This system is the primary mechanism that controls "rest and digest." The parasympathetic part is dominant in rest conditions, especially when an organism progresses from states of energetic exacting stress to a rest state.

Output	Preganglionic	Ganglion	Postganglionic	Effector
Cranial part				
Ncl. Edinger-Westphal	N. oculomotorius (III. cranial nerve) and its ramus inferior	Ggl. ciliare	Nn. ciliares breves	M. sphincter pupillae (miosis) and *M. ciliaris* (accommodation)
Ncl. salivatorius superior	N. facialis (VII. cranial nerve) and branch of n. petrosus major	Ggl. pterygopalatinum	Nn. pterygopalatini N. zygomaticus N. lacrimalis	Tear gland
	N. facialis (VII. cranial nerve), chorda tympani, and n. lingualis	Ggl. submandibulare	Nn. lingualis	Submandibular and sublingual salivary glands
Ncl. salivatorius inferior	N. glossopharyngeus (IX. cranial nerve) and branches of n. petrosus minor and n. tympanicus	Ggl. oticum	N. auriculotemporalis	Parotid gland
Ncl. dorsalis n. vagi	N. vagi (X. cranial nerve)	Intramural ganglia in the heart and in the respiratory and digestive systems	N. vagi (X. cranial nerve)	
Sacral part				
Ncl. intermediolateralis			Plexus hypogastricus inferior	

4. Sympathetic division

From an anatomical perspective, the sympathetic division represents the thoracolumbal component of the autonomic nervous system. This system is the primary mechanism that controls the "fight-or-flight" response. The sympathetic part is dominant in stressful situations, especially when an organism prepares for situations associated with high-energy output.

Axons of neurons C8–L3 (nucleus [ncl.] intermedial and ncl. intermediolateralis) leave the spinal cord by the ventral roots of the rami *communicantes albi* and enter the sympathetic trunk. In this part, most neural connetions are placed. Only a part of the neuron is interconnected in the prevertebral ganglia. Ganglionic fibers proceed to the organs either through the *rami viscerales* (from the sympathetic trunk) or through the *rami communicantes grisey* and further by sensory neurons to the periphery (especially the skin). Fibers from the rami viscerales proceed most often periarteriorlarly.

5. Neurotransmitters and receptors of the autonomic nervous system

Acetylcholine binds to two types of membrane receptor: muscarinic and nicotinic. Muscarinic receptors are located on the membranes of effector cells, between the terminals of the postganglionic parasympathetic and sympathetic cholinergic fibers and effector organs. Their activation exhibits a slower excitatory effect. Nicotinic receptors are localized to the membranes of ganglionic parasympathetic and sympathetic neurons, and their activation exhibits a rapid depolarization-excitatory effect on ganglionic neurons.

Noradrenaline is a neurotransmitter of the sympathetic part of the autonomic nervous system. It binds to two types of membrane receptors: α-adrenergic and β-adrenergic. The results of the combinations are different responses of the effector organs. For example, stimulation of α-receptors on vessel smooth muscle induces vasoconstriction, while stimulation of β-receptors of bronchial smooth muscle induces bronchodilatation.

There are inhibitory and excitatory synapses between neurons. Relatively recently, the third subsystem of neurons, known as non-adrenergic, non-cholinergic transmitters (because they use nitric oxide as a neurotransmitter), has been described and found to be integral to autonomic function, particularly in the gut and lungs [8].

6. Mechanism of action

α_1-*Receptors* are found in the vascular smooth muscle of the skin and splanchnic region, in the sphincters of the gastrointestinal tract and bladder, and in the radial muscle of the iris:

1. The α_1-receptor is embedded in the cell membrane, where it is coupled via a G_q protein to phospholipase C. In the inactive state, the α_q subunit of the heterotrimeric G_q protein is bound to GDP.

2. When an agonist, such as noradrenaline, binds to the α_1-receptor, a conformational change occurs in the α_q subunit of the G_q protein that has two effects: GDP is released from the α_q subunit and replaced by GTP, and the α_q subunit (with GTP attached) detaches from the rest of the G_q protein.

3. The α_q-GTP complex migrates within the cell membrane and binds to and activates phospholipase C. Intrinsic GTPase activity then converts GTP back to GDP, and the α_q subunit returns to the inactive state (not shown).

4. Activated phospholipase C catalyzes the liberation of diacylglycerol and IP_3 from phosphatidylinositol 4,5-diphosphate. The IP_3 that is generated causes the release of Ca^{2+} from intracellular stores in the endoplasmic or sarcoplasmic reticulum, resulting in an increase in intracellular Ca^{2+} concentration. Together, Ca^{2+} and diacylglycerol activate protein kinase C, which in turn phosphorylates proteins. These phosphorylated proteins execute the final physiological actions, such as contraction of smooth muscle.

α_2-Receptors are less common than α_1-receptors; they are found in the walls of the gastrointestinal tract and in presynaptic adrenergic nerve terminals:

1. The agonist (noradrenaline) binds to the α_2-receptor, which is coupled to adenyl cyclase by an inhibitory G protein (G_i).

2. When noradrenaline is bound, G_i protein releases GDP and binds to GTP, and the α_i subunit dissociates from the G protein complex.

3. The α_i-subunit then migrates in the membrane and binds to and inhibits adenyl cyclase. As a result, cAMP levels decrease, producing the final physiological action. For example, activation of α_2-receptors in the wall of the gastrointestinal tract causes relaxation.

β_1-Receptors are prominent in the heart (increase in activity), in the saliva glands (increase in secretion), in the adipose tissue, and in the kidney (where they promote renin secretion).

β_2-Receptors are found in the vascular smooth muscle of skeletal muscle, in the walls of the gastrointestinal tract and bladder, and in the bronchioles. The activation of β_2-receptors in these tissue leads to relaxation or dilatation:

1. β_2-Receptors are embedded in the cell membrane. They are coupled, via a G_S protein, to adenylyl cyclase. In the inactive state, the α_S-subunit of the G_S-protein is bound to GDP.

2. When an agonist, such as noradrenaline, binds to the β_2-receptor, a conformational change occurs in the α_S-subunit. This change has two effects: GDP is released from the α_S-subunit and replaced by GTP, and the activated α_S-subunit detaches from the G protein complex.

3. The α_S-GTP complex migrates within the cell membrane and binds to and activates adenylyl cyclase. GTPase activity converts GTP back to GDP, and the α_S subunit is returned to its inactive state.

4. Activated adenylyl cyclase catalyzes the conversion of ATP to cAMP, which serves as the second messenger. cAMP, via the steps involving activation of protein kinases, initiates the final physiological actions.

Nicotinic receptors are found in several important locations: on the motor end plate of skeletal muscle, on all postganglionic neurons of both the sympathetic and parasympathetic nervous systems, and on the chromaffin cells of the adrenal medulla:

1. The nicotinic receptor for acetylcholine is an ion channel for Na^+ and K^+. The receptor has five subunits: two α, one β, one δ, and one γ. These five subunits form a funnel around the mouth of a central core. When no acetylcholine is bound, the channel is closed.

2. When acetylcholine is bound to each of the two α-subunits, a conformational change occurs in all of the subunits, resulting in opening of the central core of the channel. When the core of the channel opens, Na^+ and K^+ flow down their respective electrochemical gradients.

Muscarinic receptors are located in all of the effector organs of the parasympathetic nervous system: in the heart, gastrointestinal tract, bronchioles, bladder, and male sex organs. These receptors also are found in certain effector organs of the sympathetic nervous system, specifically, in sweat glands:

1. Some muscarinic receptors have the same mechanism of action as α_1-adrenoreceptors. In these cases, binding of acetylcholine to the muscarinic receptor causes dissociation of the α-subunit of the G protein, activation of phospholipase C, and production of IP_3 and diacylglycerol. IP_3 releases stored Ca^{2+}, and increased intracellular Ca^{2+} with diacylglycerol produces tissue-specific physiological actions.

2. Other muscarinic receptors alter physiological processes via direct action of the G protein. In these cases, no other second messenger is involved. For example, muscarinic receptors in the cardiac sinoatrial node, when activated by Ach, produce activation of a G_i-protein and release of the α_I-subunit, which binds directly to the K^+ channel of the sinoatrial node. When the α_I-subunit binds to K^+ channels, the channels open, slowing the rate of depolarization of the sinoatrial node, and decreasing heart rate.

7. Autonomic nervous system: autonomic centers

Centers of the autonomic nervous system are regarded to be integrators of responses to internal and external stimuli that are related to the control of autonomic functions. From this perspective, there are probably no autonomic centers in the spinal cord, although all sympathetic and sacral parasympathetic fibers extend outward from the spinal cord. It is not clear whether there are centers controlling and coordinating the activities of the relevant parts of the autonomic nervous system or whether they are only peripheral centers. Similarly, the importance of the brain cortex, which is involved in the control of autonomic functions, lies in the integration and generation of conditioned reflexes associated with the autonomic nerves.

Regarding the *brainstem* and *hypothalamus*. Reticular formation is responsible for the regulation of the cardiovascular and respiratory systems and is the center of some autonomic reflexes. The cardiovascular center includes the following structures:

- The ncl. dorsalis n. vagi is the source of vagal parasympathetic afferentation.

- The pressoric area is located on both sides of the dorsolateral part of the reticular formation. Increased activity leads to an increase in blood pressure. Sympathetic preganglionic neurons innervating the heart, blood vessels, and juxtaglomerular apparatus are efferent pathways from this center.

- The depressoric area is located in the ventromedial part of both sides of the reticular formation. Increased activity leads to decrease in blood pressure and, reciprocally, is connected to the pressoric area.

- The respiratory center is functionally situated in the autonomic centers because it affects the spinal motor neurons controlling breathing movements through the autonomic respiratory rhythm generator and inspiration rhythm.

- The autonomic reflexes are associated with input and processing of food. It is a reflex encompassing sucking, swallowing, salivation, secretion of gastric and pancreatic juices, and vomiting.

8. Hypothalamus

The function of the hypothalamus is highly complex; in fact, there is no important activity in the body that is not regulated in some way by the hypothalamus.

8.1. Center of hunger and satiety

The satiety center is located near the regulatory centers for secretion of hormones and endocrine processes in the body. The center of hunger is located near the center of satiety. Hunger is a feeling (unconditioned reaction of the body) caused by the lack of food. It is an important signal and one that prompts the body about the need for food intake and the energy from it. Hunger occurs when blood glucose levels fall below a certain level. The need for food intake is also influenced by signals from the digestive system and, by the action of certain hormones, state of mind and/or state of attention, among others, may play a role. Feelings of hunger vary among individuals, with different speeds and intensities, and are tolerated differently—some tolerate hunger well, while in others, it is associated with mood changes manifesting as irritability or fractiousness. Prolonged starvation leads to elimination of psychological barriers and principles (e.g., cannibalism from situational emergency), with hallucinations or paranoia.

8.2. Control of food intake

It is assumed that the information from the periphery (sensory inputs from the digestive tract, including gustatory afferentation) is guided into the ncl. arcuatus in the hypothalamus, where

there are projections into the lateral part of the hypothalamus: ncl. paraventricularis and ncl. dorsomedialis. All of these structures contain two types of neurons: orexigenic, which synthesize substances, of which higher levels correlate with increased ingestion of food and activate the ncl. ventromedialis, and anorexigenic, which synthesize substances, of which higher levels correlate with reduced intake of food.

8.3. Center of thirst

Thirst is the body's response to a lack of fluids, and there are two types of dehydration. The first type is the shortage of water (mostly in well-trained athletes, who secrete thin "water" sweat). In this case, the blood is concentrated, but only briefly, because water from the intercellular spaces immediately starts to flow into the blood, resulting in increases in salt concentration in the extracellular fluid. In response, water from cells moves into the intercellular spaces and, thus, results in partial dehydration. The second type of dehydration is not only the loss of water but also a large amount of salts (untrained athletes secrete dense "salty" sweat), which are mainly in the blood and in the extracellular fluids. This usually results in only a slight increase in the concentration of ions (salts) in the extracellular fluid. In this type of dehydration, water content in the cells remains stable; however, the amount of circulating blood and intercellular fluid is reduced.

The ncl. paraventricularis contains cells that are in the contact with blood flow and cerebrospinal fluid and respond either by initiating thirst or, conversely, by initiating the urge to urinate. Stimuli are from osmoreceptors (on cue from increases in osmotically active substances in the extracellular fluid), from the renin-angiotensin system (decreased plasma volume; greater concentrations of angiotensin II elevate blood pressure and cause the feeling of thirst) and baroreceptors (decrease in plasma volume). If there is a fluid deficiency in the body, the pressure in the veins is small, and blood becomes too "dense."

8.4. Control of body temperature

The preoptic area in the hypothalamus is responsible for monitoring body temperature and for reactions to increases in temperature. Extreme increases in temperature are apparent when this area is injured or damaged. The area hypothalamica posterior contains neurons that do not directly monitor body temperature; however, they react to the information from peripheral and central thermoreceptors and activate output functions of thermoregulation. Output functions of thermoregulation are concentrated on the maintenance of adequate body temperature and protection of the organism against hypothermia.

8.5. Control of the endocrine glands

Control through the hypothalamic-hypophyseal tract (ncl. paraventricularis and ncl. supraopticus—antidiuretic hormone and oxytocin) and hypothalamic sympathetic fibers influences adrenaline and noradrenaline secretion. The hypothalamus also controls the secretory activity of the anterior pituitary gland through the release of liberins and inhibitory (inhibins) factors.

8.6. Relationship with sexual function

The hypothalamus has an association with all sexual activities including sexual development, the menstrual cycle, ovulation, erection, copulation, ejaculation, pregnancy, birth, lactation, and sexual urges and behavior. Injury to the anterior hypothalamus results in disordered libido, while injury to the posterior hypothalamus results in increased sexual urges.

8.7. Control of emotions

Emotions are psychological processes that involve subjective experiences of comfort and discomfort linked to physiological changes (changes in heart rate and respiratory rate), motor manifestations (mimics, gesticulation), change readiness, and concentration. Emotions induce and influence other psychological processes. Hypothalamic nuclei, together with the anterior nuclei of the thalamus and cingulate gyrus, form the Papez circuit, which is an important part of the limbic system. They represent a very close structural relationship and, thus, represent the basis for the formation of autonomic manifestations of emotion.

8.8. Control of biological rhythms

Rhythmic activity is generated by the ncl. suprachiasmaticus. Rhythmic hypothalamic processes extend into practically all other functions of the hypothalamus as sympathetic tone, hormone secretion, regulation of temperature, intake of food and fluids, sexual function, emotion, and immune processes.

Other relationships include relation to sleep (sleep center in the anterior hypothalamus and center of wakefulness in the posterior hypothalamus), immunity (mediated by changes in the production of hormones [glucocorticoid production]), and changes in the tone of the autonomic nervous system. Sympathetic-immune interactions particularly affect the secondary lymphoid organs (spleen, lymph nodes) and are believed to increase preparedness for escape/attack. Relation to memory (Papez's circuit—transmission of short-term to long-term memory), complex behavior (motivations, emotions), control of metabolism (through control of the endocrine glands—secretion of adrenaline, adrenocorticotropic hormone, etc.), sensory function and relation to the motor system ninvoluntary movements, extrapyramidal tract, basal ganglia).

9. Clinical practice

Disorders of the autonomic nervous system result in relatively serious neurological conditions. For example, excessive activation of the sympathetic nervous system by emotions, painful stimuli, and drops in blood pressure, such as hemorrhagic shock or hypoglycemia, trigger a prepared stress response from the body. Chronically increased sympathetic activity (sleep deprivation and social insecurity, among others) can lead to psychosomatic disorders

such as hypertension, type 2 diabetes mellitus, and/or gastric ulceration. Hypothalamic disorders can cause damage to thermoregulation, circadian rhythms, insomnia, the menstrual cycle, premature maturation, growth disturbances, eating disorders (aphagia and subsequent anorexia, hyperphagia may develop), or hormone production disorders [6].

Therefore, proper and early diagnosis of autonomic nervous system disorders forms the basis of successful treatment. Symptoms that indicate autonomic system disorders include sweating, digestive disorders, dizziness, changes in heart rate, or urinary problems. Objectively, the autonomic nervous system can be investigated using classical and special methods. Classical methods include, in particular, the examination of cardiovascular reflexes, Valsalva maneuver, orthostatic test, or deep breathing. These tests do not, however, evaluate the extent of dysfunction [9]. Currently, a special method for examining autonomic nervous system activity involves the measurement of heart rate variability. This is a parameter that reflects the current functional state of the autonomic nervous system. In recent years, heart rate variability measurement has also attracted attention outside of research in everyday clinical and outpatient practice and in health promotion [10]. Parameters of heart rate variability are able to provide information about the proportion of sympathetic and parasympathetic components with respect to respiration or thermoregulation. Heart rate is also affected by many other factors that can increase sympathetic tone, for example, male sex, younger age, and violent emotions. Female sex, older age, or good physical condition may be involved in reducing heart rate. Heart rate variability determination is performed using time or spectral analysis methods.

From this perspective, detailed study of the functions and mechanisms of the autonomic nervous system is important and necessary.

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